No. 2025-1236

United States Court of Appeals for the Federal Circuit

EXELIXIS, INC.,
Plaintiff-Appellee

v.

MSN LABORATORIES PRIVATE LTD., MSN PHARMACEUTICALS, INC.
Defendants-Appellants

Appeal from the U.S. District Court for the District of Delaware, Case No. 1:22-cv-00228-RGA, Judge Richard G. Andrews

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REPLY BRIEF FOR DEFENDANTS-APPELLANTS

EIMERIC REIG-PLESSIS
Winston & Strawn LLP
101 California Street
San Francisco, CA 94111
(415) 591-6800
ereigplessis@winston.com

KURT A. MATHAS
BRYCE A. COOPER
KEVIN J. BOYLE
Winston & Strawn LLP
35 W. Wacker Drive
Chicago, IL 60601
(312) 558-5600
kmathas@winston.com
bcooper@winston.com
kjboyle@winston.com

Counsel for Defendants-Appellants

CERTIFICATE OF INTEREST

Undersigned counsel certifies that the following information is accurate and complete to the best of counsel's knowledge:

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.
MSN Laboratories Private Ltd.	N/A	None
MSN Pharmaceuticals, Inc.	N/A	MSN Laboratories Private Ltd.

4. **Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

Winston & Strawn LLP: George C. Lombardi, Elizabeth E. Grden, Brian L. O'Gara

Heyman Enerio Gattuso & Hirzel LLP: Dominick T. Gattuso, Brendan P. McDonnell

5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

Yes

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

None/Not Applicable

/s/ Bryce A. Cooper
BRYCE A. COOPER
Counsel for Defendants-Appellants

August 1, 2025

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GLOSSARY OF ABBREVIATIONS

’015 patent	U.S. Patent No. 11,098,015 (Appx191-239)
’349 patent	U.S. Patent No. 11,298,349 (Appx73-92)
’439 patent	U.S. Patent No. 11,091,439 (Appx93-141)
’440 patent	U.S. Patent No. 11,091,440 (Appx142-190)
’473 patent	U.S. Patent No. 7,579,473 (Appx2843-3051)
’549 patent	U.S. Patent No. 9,809,549 (Appx10630-10676)
’776 patent	U.S. Patent No. 8,877,776 (Appx10583-10629)
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
^{13}CNMR	carbon-13 nuclear magnetic resonance
Donovan	Dr. Maureen Donovan, MSN’s pharmaceutical formulation expert
DSC	differential scanning calorimetry
Exelixis	Plaintiff-Cross-Appellant Exelixis, Inc.
FDA	U.S. Food and Drug Administration
Koleng	Dr. John Koleng, Exelixis’ pharmaceutical formulation expert
Lepore	Dr. Salvatore Lepore, MSN’s pharmaceutical impurity expert
MacMillan	Dr. David MacMillan, Exelixis’ organic impurity expert
Malate salt patents	The ’439, ’440, and ’015 patents

MSN	Defendants-Appellants MSN Laboratories Private Ltd. and MSN Pharmaceuticals, Inc.
Myerson	Dr. Allan Myerson, Exelixis' pharmaceutical formulation expert
NDA	New Drug Application
POSA	person of ordinary skill in the art
ppm	parts per million
PTO	U.S. Patent and Trademark Office
Shah	Dr. Khalid Shah, Sr. Vice President, Exelixis
Steed	Dr. Jonathan Steed, MSN's pharmaceutical salt formation and characterization expert
TGA	thermogravimetric analysis
Trout	Dr. Bernhardt Trout, Exelixis' pharmaceutical salt formation and characterization expert
Wilson	Dr. Jo Ann Wilson, Fmr. Vice President, Exelixis
XRPD	X-Ray Powder Diffraction

INTRODUCTION

Malate salt patents. Abandoning its principal argument to the district court (Appx22), Exelixis now concedes that the malate salt patents claim a genus of all "crystalline" cabozantinib (L)-malate salts, which undisputedly requires the specification to describe "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus" or a "representative number of species." Br. 30 (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010)). Exelixis cannot meet either prong to show possession of the broad genus it claimed.

As to common structural features, the specification provides only threadbare disclosure of (1) cabozantinib (L)-malate's *chemical* formula, (2) the word "crystalline" itself, and (3) *methods* of producing the only two crystalline forms Exelixis invented, N-1 and N-2. Appx23-25; Br. 24-25. As Exelixis admits, the chemical formula "[o]f course" applies equally to *amorphous* forms (Br. 34) and thus is not "sufficient to distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350. It is equally undisputed that the disclosed methods of preparation "are not common

structural features"—and, regardless, include only "methods of preparing N-1 and N-2," not the rest of the genus. Br. 36.[1]

Exelixis' argument thus collapses to a single word, "crystalline," and is entirely circular: The specification describes common structural features to visualize or recognize all "crystalline" cabozantinib (L)-malate salts, according to Exelixis, because the specification refers to cabozantinib (L)-malate salts that are "crystalline." That is not the law. "To satisfy the written description requirement in the case of a chemical or biotechnological genus, *more than a statement of the genus is normally required*." *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1126 (Fed. Cir. 2008). That general rule is especially pertinent here, where "the complexity and [un]predictability of the relevant technology" is undisputed. *See Ariad*, 598 F.3d at 1351.

It is no answer that "[t]he maximum potential size of any *pure* polymorph genus is fourteen forms." Br. 4 (quoting Appx21). The asserted claims are not limited to "pure" forms—a "very high standard of characterization"—nor do they exclude solvates, which fall outside the 14-form limit for "pure" forms characterized by single-crystal chromatography.

[1] All emphases are added unless otherwise noted.

Appx1919(545:19-547:1); Appx1923(561:20-562:7) (Steed). As Exelixis' own expert admitted, "[t]he range and combinations of crystal growth structures are *virtually infinite*." Appx2066(922:10-17) (Trout). Exelixis tries to diminish this admission by contending it refers only "to prior art without the benefit of Exelixis' teachings" (Br. 41), but the patents here lack any "teachings" about the size of the genus—instead, they describe only *two* related species. *See* Br. 10-11.

Exelixis falls back to a generic definition of "crystalline" material as having a "regular repeating underlying arrangement of molecules" (Br. 3), but that is no different than the "crystalline" label itself, and the argument misses the point. Polymorphs undisputedly have "*different* internal crystal structures and, therefore, possess *different* physico-chemical properties." Appx3894. Exelixis identifies no specific commonalities in the internal crystal structures of polymorphs within the claimed genus, or any commonalities in their resulting physico-chemical properties. Whether those properties are "unclaimed" (Br. 4) is irrelevant here. All agree that polymorphs are necessarily identified and characterized by their physical properties, and Exelixis repeatedly touts the purported

utility of the two crystalline forms it discovered, including "improved stability and solubility." Br. 2; *see also, e.g.*, Br. 10, 45.

Unable to satisfy the relevant test, Exelixis attacks a strawman, arguing that enforcing the written-description requirement would make it "impossible to claim a genus" (Br. 33) and require "Exelixis to disclose all species" (Br. 43). Not so. This appeal is limited to the unique situation of a patentee claiming all "crystalline" forms in a highly unpredictable field, with undisclosed species exhibiting vastly different properties. Reversal would not threaten patents on novel compounds and "pharmaceutical salts thereof." Br. 47. Indeed, Exelixis obtained (and successfully asserted) a compound patent on cabozantinib "or a pharmaceutically acceptable salt thereof," which expires in 2026. Appx11743.

GSK is thus inapposite. There, the compound "[d]utasteride [wa]s where the novelty lies," and there was "no dispute that a solvate of dutasteride has the same effective chemical function of dutasteride." *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 2013 WL 4082232, at *6 (D. Del. Aug. 9, 2013), *aff'd*, 744 F.3d 725 (Fed. Cir. 2014). In contrast, here, the claimed crystalline forms are both a point of novelty and critical to whether the invention will work. *See* Appx37 (accepting Exelixis'

argument that there was no "reasonable expectation of success of forming a *crystalline* salt") (emphasis in original); Appx2066(923:14-924:1) (Trout agreeing "not every polymorph" may have therapeutic effect).

The malate salt patents are classic examples of litigation-inspired overreach. As Exelixis admits, it filed their applications "[w]hile *MSN I* was ongoing" (Br. 14)—i.e., *during litigation* against MSN on the earlier-filed parent patent limited to form N-2. It does not matter that Exelixis filed the applications "before *judgment*." Br. 4. By then, Exelixis knew of MSN's noninfringement defense that its generic product uses the undisclosed form S. Nor does it matter that the original PCT application included broad genus claims. Br. 9. As Exelixis admits, it did not pursue those broad claims but instead "chose to pursue narrow claims to Forms N-1 and N-2 first" (*id.*)—the only two forms that Exelixis invented. It was only *after* MSN invented and disclosed form S that Exelixis filed the applications from which the malate salt patents issued to obtain broader genus claims to preempt the field.

As to representative species, Exelixis repackages the same argument—asserting that N-1 and N-2 are representative merely because "they are crystalline." Br. 26. For the same reasons as the common-

structural-features prong, Exelixis' argument fails. The Court should thus reverse, or at least vacate, because these two "disclosed species only abide in a corner of the genus." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

'349 purity patent. For the sole asserted claim of the '349 patent—claim 3—the only limitation that Exelixis disputes would have been obvious is the "essentially free" limitation, which requires <200 ppm of the 1-1 impurity.[2] Br. 5. Clear and convincing evidence showed that the Brown prior art inherently achieves this limitation, as confirmed by three batches prepared by Regis—Exelixis' own contract manufacturer.

On appeal, Exelixis relies on two findings to defend the judgment of no inherency: (1) the district court's *sua sponte* conclusion that "the Regis batches did not follow the Brown process"; and (2) the district

[2] Exelixis has now dropped its cross-appeal challenging the district court's judgment that MSN does not infringe the '349 patent. Dkt. 26. Since the judgment, however, Exelixis has obtained and asserted a continuation patent that omits the '349 patent's "glidant" limitation, which was the basis for the district court's noninfringement ruling. *See* No. 1:25-cv-00346-RGA (D. Del., filed Mar. 19, 2025). MSN thus maintains its obviousness challenge to the '349 patent, which may be relevant to the new continuation patent.

court's speculation that "the 1-1 impurity can form as a degradation product." Br. 53-54 (cleaned up). Neither finding supports the judgment.

First, as Exelixis repeatedly conceded before the district court, Regis *did* follow the Brown process and obtained cabozantinib essentially free of the 1-1 impurity each time. Exelixis never disputed those facts until this appeal. Both sides' experts also confirmed that Regis followed Brown, and Exelixis cites no evidence of any material deviation.

Second, the notion that some amount of 1-1 impurity "*can form*" as a degradation product is immaterial because claim 3 of the '349 patent does not exclude degradation—it undisputedly *allows* up to 200 ppm of the 1-1 impurity from degradation or otherwise. Like the district court, Exelixis legally errs by demanding more from Brown than what the '349 patent requires.

This Court should thus reverse the judgment and hold all asserted claims invalid or, at the very least, vacate and remand.

ARGUMENT

I. The asserted claims of the malate salt patents are invalid for lacking written description.

Exelixis does not dispute that the malate salt patents claim a genus or that the district court correctly held "'[a]ll crystalline cabozantinib (L)-

malate salts fall within [the] scope' of the asserted claims." Appx20. This requires the specification to describe "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus" or a "representative number of species." Br. 30 (quoting *Ariad*, 598 F.3d at 1354). Exelixis' response fails to meet either prong to show written-description support.

A. The specification fails to disclose structural features to distinguish the genus of crystalline cabozantinib (L)-malate and to visualize or recognize its members.

1. The district court legally erred by crediting "a broad outline of [the] genus's perimeter."

Exelixis does not dispute that the district court relied on only three factual findings to conclude the claims are adequately described by the specification's disclosure of "[1] the chemical name and formula of cabozantinib (L)-malate, as well as [2] that the structure is crystalline," and "[3] general methods of forming a crystalline salt," along with "methods of preparing the N-1 and N-2 form." Appx24; *see also* Appx25. Exelixis argues that these findings are sufficient if they are not considered "piecemeal." Br. 33. But none of them—individually or collectively—describe sufficient "structural features" to support broad genus claims to all crystalline cabozantinib (L)-malate salts.

First, Exelixis concedes that the "chemical name and formula of cabozantinib (L)-malate" does not differentiate crystalline from amorphous forms. Br. 33-34. So, while *Ariad* recognizes these features *may* support a "precise definition" that satisfies "an adequate written description" in *some* chemical genera, they offer no value here. 598 F.3d at 1350.

Second, Exelixis contends that the term "crystalline" "resolves the alleged ambiguity" of the common chemical name and formula and "defines a common structural attribute" of the members of the genus. Br. 34, 36. But nothing in *Ariad* suggests that identifying a single common structural attribute automatically provides sufficient disclosure for an entire genus when it merely offers "[a] broad outline of a genus's perimeter." *Regents of the Univ. of Minn. v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023). As Exelixis admits, "crystalline" merely means there is *some* "regular repeating underlying arrangement of molecules" (Br. 34), but that says nothing about what the underlying arrangement *is*—let alone what "physical properties, or other properties" result from any such arrangement. *See Ariad*, 598 F.3d at 1350-1351.

Exelixis suggests that this concern is primarily limited to genera that are "described solely by [their] function." Br. 35 (collecting cases).

But nothing in those cases stands for that proposition, and this Court has invalidated genus claims defined by structural limitations as well. *See ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368 (Fed. Cir. 2009); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154 (Fed. Cir. 1998); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329 (Fed. Cir. 2010). Here, it is undisputed that a POSA would have no understanding of any of the other structural features or properties of species other than N-1 and N-2 based on the specification. *See also Pharmacyclics LLC v. Alvogen, Inc.*, 2022 WL 16943006, at *10 (Fed. Cir. Nov. 15, 2022) (one "can't predict in advance the physical properties that a crystalline form will have").

Nor is it sufficient that a POSA would be able—for any given sample—"to determine if a solid was crystalline." Br. 35 (citing Appx2049-2050(856:25-857:12)). That conflates what it would take to prove infringement of a known species with what is required for adequate written description for an entire genus.

Third, Exelixis defends the district court's reliance on the description of methods for preparing N-1 and N-2, because they "show possession of crystalline cabozantinib (L)-malate." Br. 36. Further, Exelixis erects a straw man by arguing that it is not required to "show possession of every

species" or "working examples of every species." Br. 36. But there is no dispute that Exelixis possessed and disclosed how to make N-1 and N-2. That does nothing "to satisfy the statutory requirement of a description of the invention," because "it is not enough for the specification to show how to make and use the invention, i.e., to enable it." *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1377 (Fed. Cir. 2017); *see also Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013) (district court legally erred by asking whether a POSA "would have been enabled" to make certain species, instead of "whether the [specification] *discloses* [other] variants to him, specifically, as something [inventors] actually invented.") (cleaned up). Exelixis offers no answer.

2. The district court legally erred by applying a less "rigorous" test for structural claim limitations.

Exelixis concedes, as it must, that "the same" written-description standard applies to both structural and functional claim limitations. Br. 37. Nevertheless, Exelixis tries to justify the district court's reasoning that "more rigorous requirements" apply to functional limitations (Appx24) by analogizing to *GSK*, while attempting to distinguish this Court's cases that held structural claim terms inadequately described.

Br. 37-45. On both fronts, Exelixis' arguments fail to rehabilitate the district court's analysis, which is legally flawed.

GSK. Exelixis misses the point in arguing that "the *GSK* decision did not turn on any 'point of novelty.'" Br. 39. Courts consider which part of an invention is novel in a written description analysis, because, as the district court in *GSK* explained, "that is where a person skilled in the art would need the most information." 2013 WL 4082232, *6, *aff'd*, 744 F.3d 725. There was no dispute that the novel dutasteride compound in *GSK* was adequately described, and this Court held that the specification's high-level discussion of solvates provided sufficient written description and "match[ed] the claim scope," because steroid solvates were well-known in the art and "the universe of solvents thought to be pharmaceutically acceptable was well-known and relatively small." 744 F.3d at 728. Moreover, Exelixis is wrong that the specification "did not have examples of dutasteride solvates." Br. 38. The district court characterized Example 3D as identifying a "reacted" solvate. *GSK*, 744 F.3d at 728-729.

By contrast, here, the novelty and alleged utility of the claimed crystalline forms lies in their "properties relating to processing, manufacturing, storage stability, and/or usefulness as a drug," which

distinguishes them from the prior art. Appx127(3:22-23). Exelixis argues that these "features" are not explicitly limited only to Forms N-1 and N-2, presumably relying on the specification's broad definition of Compound (I). Br. 40. But Exelixis does not—and cannot—dispute that the data supporting the specification's assertions is from testing *only* on the two disclosed crystalline forms, N-1 and N-2. Appx128-Appx129(6:56-8:24); *see also* MSN Br. 16-17, n.5. Nor does Exelixis dispute that those same properties *cannot* be expected in other forms. Appx1939(626:14-23) (Shah) ("Generally speaking, yes. Different polymorphs can have different characteristics" and "different properties"); Appx2065(917:6-21) (Trout) ("In general, [properties of polymorphs] can differ.").

There is also no parallel between the "well-known and relatively small" genus of pharmaceutically acceptable solvents giving rise to the claimed solvates in *GSK* and the claims here, which cover all possible unknown and unpredictable polymorphs of cabozantinib (L)-malate. (Appx2066(922:12-17) (Trout)). Exelixis tries to walk back Dr. Trout's testimony that the number of species in the genus is "virtually infinite," recharacterizing it to supposedly refer to the number of "crystalline structures available generally." Br. 41. But the record is clear. Dr. Trout

previously opined that the N-2 patent was non-obvious, supported by his contention that "there was no way a POSA would have had any reasonable expectation of … which solid form, if any, would be obtained, nor any reasonable expectation of preparing the N-2 crystalline form." Appx2066(922:3-9). It was in support of that opinion on N-2 that he explained that "[t]he range and combination of crystal growth structures are virtually infinite." Appx2066(922:12-17).

Exelixis also attempts to narrowly portray the genus by arguing that the maximum potential size of any pure polymorph genus is fourteen forms. Br. 41. But Dr. Steed explained that number referred to pure forms "characterized by single crystal crystallography," a "very high standard of characterization" (Appx1919(545:19-546:7)), and did not include solvates (Appx1923(561:20-562:7)). Exelixis responds that solvated forms have not yet been identified and characterized. Br. 42, n.8. But that is immaterial to whether the specification provides sufficient written description for them. *See PureCircle USA Inc. v. SweeGen, Inc.*, 2024 WL 20567, at *4 (Fed. Cir. 2024) (recognizing in written description analysis invalidating claims that "potentially additional unknown" species could fall within the claimed genus). Here, the asserted claims are

undisputedly not limited to pure forms of crystalline cabozantinib (L)-malate and *include* any solvates, further highlighting the breadth and dissimilarity of the covered species.

Finally, Exelixis contends that the "claims upheld in *GSK* cover any crystalline form of the solvates, just like the claims at issue here cover any crystalline form of the cabozantinib (L)-malate." Br. 42. Setting aside that the Court in *GSK* did not reach the arguments presented here, because the defendants "presented a limited issue" on whether the specification sufficiently disclosed "solvates" prepared by three different methods, 744 F.3d at 729, Exelixis' comparison is inapt. In *GSK*, the "'solvates' of dutasteride [were] not distinguished by a particular performance property" and "the specification itself suggest[ed] that any one of the solvate forms will suffice equally." *Id.* at 731. That is not the case here. Different forms of cabozantinib (L)-malate *are* undisputedly distinguishable by many different physico-chemical and performance properties, which "can affect the manufacturability, performance, and quality of a drug product." Appx2060(897:2-4) (Trout); *see also* Opening Br. 16-17, 19-22.

GSK, therefore, is inapposite. It does not diminish the written-description requirement for structural limitations—let alone for structure that is part of the point of novelty and critical to the invention's utility.

ICU Medical and Entresto. Exelixis fails to defend the district court's error in believing that this Court in *ICU Medical* found a functional limitation in the "spikeless" claims it invalidated. Appx27. Rather, it was the "spike" claims that were found to have a functional (i.e., "for piercing the seal") component. 558 F.3d at 1376. The Court made clear that it referred to the "spikeless" claims "not because they exclude the preferred embodiment of a valve with a spike but rather because these claims do not include a spike limitation, i.e., they *do not require* a spike." *Id.* In other words, there was no functional uncertainty as to *those* claims—they "generically[] cover[ed] those valves that operate with a spike and those that operate without a spike." *Id.* at 1378. And as Exelixis concedes, "[s]piked and spikeless medical valves have different *structural* features, based on whether they included the spike element." Br. 42-43. Similarly, the specification here fails to describe the *structure* of any crystalline form lacking the identifying properties unique to N-1 and N-2. Appx2061(904:13-15) (Trout).

Exelixis also claims that MSN "incorrectly characterizes" the timing of the malate salt patents and that MSN's invention of form S, without more, "does not cast doubt" on the written description of Exelixis' claims in view of this Court's ruling in *In re Entresto*, 125 F.4th 1090 (Fed. Cir. 2025). Br. 49. But that misapprehends the point. There is no dispute that the malate salt patent applications were filed after Exelixis received notice that MSN did not infringe the N-2 patent—four years *before* the district court's 2023 judgment. *Exelixis, Inc. v. MSN Labs. Pvt. Ltd. & MSN Pharms, Inc.*, No. 19-cv-2017-RGA-SRF, ECF No. 1, at ¶ 23.

There are clear parallels to the "overzealous" litigation recognized by this Court in *ICU Medical*. 558 F.3d at 1379. There, like here, the plaintiff's continuation application was filed *10 years* after the priority application. *Id.* at 1377. And it sought broad genus claims based on the *same* specification that described a species the plaintiff invented, long after it was on notice that the defendant did not infringe that earlier species patent. *Id.*

Entresto does not change the result. *Entresto* did not analyze the claimed invention as a genus and did not apply *Ariad*'s test for possession of a genus claim that requires either "a representative number of species"

or sufficient structural features to "'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350; *cf. Entresto*, 125 F.4th at 1097-1100 (analyzing both written description and enablement without any genus-species analysis). Here, however, Exelixis no longer disputes that the malate salt patents claim a genus of crystalline forms, triggering *Ariad*'s two-prong test. *See* Br. 3-4, 30.

Regardless, the mere fact that a genus claim is "part of the original disclosure" does not mean it provides "an adequate and enabling description of all [members of the genus]." *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1346-47 (Fed. Cir. 2005).

Tronzo and Eli Lilly. Exelixis does not dispute that both cases invalidated broad genus claims that were defined by structural and not functional limitations, where the patentees failed to disclose sufficient structural features that were common to the species within the genus. *Tronzo*, 156 F.3d 1154; *Eli Lilly*, 619 F.3d 1329. Exelixis tries to distinguish them because the specifications either "tout[ed] the advantages" of, or "addressed only," one species in a broadly claimed genus. Br. 44-45 (quoting *Tronzo*, 156 F.3d at 1159, *Eli Lilly*, 619 F.3d at 731). But that is exactly what the malate salt patents do for N-1 and N-2. The specification

may broadly define "Compound (I)" to include all amorphous and crystalline forms of cabozantinib (L)-malate. *See* Appx129(7:10-26). But the data supporting the alleged utility of beneficial pharmaceutical properties for development relate to N-1 and N-2 only. *E.g.*, Opening Br. 16-17.

3. The district court legally erred in discounting differences in physical properties among members of the claimed genus.

Exelixis does not dispute MSN's evidence that different crystalline forms have "different densities, melting points, solubilities, hygroscopicity, vapor pressure, and stability"; that "the properties of one crystalline form cannot be used to predict the properties of a different form"; and that "the properties of the known crystalline forms of cabozantinib (L)-malate differ." Appx25-26. Instead, Exelixis proclaims a legal doctrine that any "variability in … unclaimed properties is irrelevant." Br. 46. But neither *GSK* nor *Ariad* nor any other Federal Circuit case supports such a proposition, acknowledging that the "precise" definition required for written description varies by technology and may include "structure, formula, chemical name, physical properties, *or* other properties." *Ariad*, 598 F.3d at 1350-1351.

Further, Exelixis does not dispute that, "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963). And it has no answer to that principle being especially relevant here, where the identity and only alleged utility for the claimed polymorphs lies in their unique and beneficial physico-chemical properties. *See* Appx127(3:20-25), Appx129(7:10-45). Indeed, it was *Exelixis itself* that relied on these unclaimed properties in the specification to differentiate and claim the broad genus. Appx6571-6579 (Declaration of Khalid Shah).

4. Far from threatening legitimate genus claims, reversal would help to prevent similarly anticompetitive attempts to preempt the field.

Exelixis' hyperbolic concern that a reversal would "work a sea change in the law" (Br. 47) is incorrect. There is no parallel here to cases finding sufficient written description for claims to "pharmaceutical salts thereof." *Id.* Indeed, Exelixis obtained (and successfully asserted) a compound patent on cabozantinib "or a pharmaceutically acceptable salt thereof," which expires in 2026. Appx11743. And it already extended its patent monopoly by claiming species it invented within that genus, obtaining patents on N-1 and N-2. Appx10628-Appx10629; Appx10676.

The claims and findings in Exelixis' "pharmaceutical salts" cases are also not analogous to the claims here. In *Forest Labs., LLC v. Sigma-pharm Labs., LLC*, this Court upheld the district court's finding that claims to compositions of asenapine free base—not "pharmaceutical salts thereof"—were sufficiently disclosed. 257 F. Supp. 3d 664, 690-691 (D. Del. 2017), *aff'd*, 918 F.3d 928, 937-938 (Fed. Cir. 2019). In *BMS v. Aurobindo Pharma USA Inc.*, the district court found that—contrary to Exelixis' suggestion—preparation methods for *all* claimed species of "pharmaceutically acceptable salts of [apixaban]" were disclosed to a POSA. 477 F. Supp. 3d 306 (D. Del. 2020). And in *Merck Sharp & Dohme, LLC v. Mylan Pharms. Inc.,* it was undisputed that the specification "described every known hydrate" of the genus for DHP salts of sitagliptin and that no other hydrates existed. 2022 U.S. Dist. LEXIS 195204, at *105 (N.D. W. Va.). Further, the court did not identify any evidence—similar to the facts in *GSK*—that any other potential hydrate species within the claimed genus would have different physico-chemical or functional properties. *Id.* Exelixis' concerns about the viability of other salt genus claims are therefore unfounded.

In contrast, the decision below threatens to harm the pharmaceutical industry by providing a roadmap for other branded drugmakers to preempt all possible polymorphs of a known drug simply by disclosing the general and well-known concept of crystallinity. That result would unfairly punish competitors like MSN that perform the difficult work of diligently designing around patented polymorphs and inventing their own unique crystalline forms. This Court should enforce the written-description requirement and not permit Exelixis "to preempt the future before it has arrived." *Ariad*, 598 F.3d at 1353 (alteration omitted).

B. The specification fails to disclose a representative number of species to describe claims covering the entire genus.

On the trial record, this Court should reverse the judgment and hold that Exelixis also cannot meet the "representative species" prong of the written description test.

A claimed genus need not have "thousands" of known members, as Exelixis suggests (Br. 51), for disclosed species to be unrepresentative. *See Purecircle*, 2024 WL 20567 at *3 (single species not representative where "only one enzyme of the *potentially* vast class of UGTs" was disclosed and at least "*five* known enzymes" were shown to "come within the

scope of the claims."). The standard for what constitutes a representative number of examples in a genus will "necessarily vary depending on the context." *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1359 (Fed. Cir. 2019). Here, the undisputed unpredictability of polymorphs only reinforces the need for disclosure. *See Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1339 (Fed. Cir. 2021) ("general assertions of structural commonalities, in the context of the technology in this case, are insufficient").

Exelixis argues that *AbbVie* does not require disclosure of representative species on "every possible axis of comparison." Br. 51. But nor does it stand for the narrow proposition that only *functional* claims must show "species representative of structures that achieve that function." Br. 52. *AbbVie* rejected the argument that unclaimed features are "legally irrelevant," holding instead that a specification must "reflect the structural diversity of the claimed genus," regardless of whether such features are claimed. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298, 1301 (Fed. Cir. 2014). That should be especially true for polymorphs, which not only have structural diversity characterized by their XRPD patterns, but also because they are undisputedly

identified and characterized by their *physical* properties. Appx2065(918:17-919:23) (Trout); Appx1894(444:19-447:8) (Steed).

Finally, Exelixis cites Dr. Steed's on-the-spot response to a question from the district court at the end of his testimony that, in his opinion, each form "is only representative of itself." Br. 48. But the Court does not need to go that far to reverse, or at least vacate. Regardless of whether a patentee could disclose a sufficient number of representative species to claim a genus of crystalline forms in a different case, here it is clear that "the disclosed species only abide in a corner of the genus." *AbbVie*, 759 F.3d at 1300. The specification itself concedes its disclosure is limited to forms "possessing *similar or identical physical* and chemical *characteristics* … in accordance with the characterization information presented herein." Appx129(7:3-9).

The Court should thus reverse the judgment of written-description support for the malate salt patents. At a minimum, the Court should vacate and remand to address the representative species prong.

II. The district court's judgment that the '349 patent is not invalid as obvious should be reversed.

As to the '349 patent, Exelixis only disputes obviousness for one claim limitation—the "essentially free" limitation that requires <200

ppm of the 1-1 impurity. Attempting to support the judgment of nonobviousness, Exelixis echoes the district court's findings that (1) "the Regis batches did not follow the Brown process"; and (2) "the 1-1 impurity can form as a degradation product." Br. 53-54 (cleaned up). Exelixis further relies on (3) general evidence about its so-called "A-2" process (Br. 56, 61), which includes the Girindus batch that (unlike Regis) explicitly deviated from Brown. Exelixis' arguments fail to rehabilitate the district court's judgment, which is both legally and clearly erroneous.

A. The district court clearly erred in disregarding the undisputed fact that Regis followed the Brown process.

Before the district court, there was no dispute that "[t]he Regis [] batches were made using the process disclosed in Brown." Appx2763 (¶ 72); *accord* Appx2014(716:18-24) (Myerson). Exelixis' IND submission to FDA, both parties' experts, and Exelixis' post-trial briefing all confirmed that Regis followed the Brown process. Opening Br. 61-64.

Nevertheless, the district court, on its own accord, found that "it was not clear that the Regis process followed the Brown process." Appx50 (cleaned up). The district court based that finding solely on a stray mention of "[s]ome processing and reagent changes." Appx46; Appx10786(PTX-10). But the undisputed evidence showed there were no

changes between the Regis and Brown processes. Appx1818(336:11-16) (Lepore). And even if there were any supposed "changes," Regis "followed Brown within the variability of Brown." Appx2032(785:21-786:5) (Myerson); Appx1819(338:12-19) (Lepore). The district court's finding otherwise was clear error.

Pivoting from its concessions at trial and post-trial, Exelixis now argues that the district court had "no basis … to conclude that the three Regis batches … actually followed Brown." Br. 57. But Exelixis' own IND submission to the FDA shows that Regis precisely followed the Brown process. *Compare* Appx3115-3118, *with* Appx5852-5855; Appx1802-1803(271:23-275:21). The IND included a "step-by-step" narrative description of the Regis process, which Dr. Lepore compared side-by-side with the Brown process, concluding that the two "are virtually identical." *Id.* Regis followed the "very same process" that Brown described. Appx1802-1803(272:24-273:19) (Lepore).

Exelixis repeatedly conceded this point. Dr. Myerson agreed that "[t]he language used by Exelixis in its IND to describe how the clinical material was manufactured [by Regis] is identical to Example 1 Brown." Appx2032(786:2-7) (Myerson). And in post-trial briefing, Exelixis agreed

that the Regis "batches of cabozantinib (L)-malate [were] made with the Brown Process." Appx2719; *see also* Appx2763 (¶ 72) (same).

Exelixis does not defend that the district court reached its conclusion on its own accord, but rather suggests that its admissions were "inconsequential" because parties can generally defend a decision "on any ground that is supported by the record." Br. 58-59 n.11. That truism does not help Exelixis here because the record lacks any reliable support for the district court's conclusion, which turns on its misinterpretation of a statement in Exelixis' IND that "[s]ome processing and reagent changes were implemented for the GMP batch (Lot No. P172-27-1)." Appx3115. Based on this statement alone, the district court *assumed* that "Regis made [changes] to the Brown process." Appx50. Unrebutted expert testimony, however, showed that any "changes" did not take Regis outside the Brown process. Appx1874(364:14-365:13) (Lepore); Appx2032(785:21-786:5) (Myerson).

Exelixis mistakenly argues that "Dr. Lepore … was unable to explain what processing and reagent changes were made by Regis." Br. 57. In fact, Dr. Lepore testified that the IND's "description of the process … used in the production of the drug substance (Lot No. P172-27-1) at

Regis" *included* the "processing and reagent changes [] implemented for the GMP batch (Lot No. P172-27-1)." Appx1818(335:23-336:16) (Lepore discussing Appx3115-Appx3118). The "description of … Lot No. P172-27-1" included the "changes implemented for … Lot No. P172-27-1." *Id.* Dr. Lepore explained that this description of the manufacturing process, including its "changes," showed "the same chemistry, same schemes" and the "very same" process as the Brown process. Appx1802-1803(272:19-275:21); *compare* Appx3115-3118 *with* Appx5852-5855. Because the description was identical to the Brown process, Dr. Lepore concluded: "[a]ccording to that document, there were no changes" compared to Brown. Appx1818(336:11-16); *see also* Appx1819(337:22-338:3) (Lepore).

Even if there were any "changes," Dr. Myerson agreed that Regis "followed Brown within the variability of Brown." Appx2032(785:21-786:5). Ignoring that admission, Exelixis argues that Dr. Myerson testified at trial that "there were deviations" in the Regis process compared to Brown. Br. 57 (citing Appx2033(790:6-10)). But Dr. Myerson admitted that he "testified at [his] deposition differently." Appx2033(790:11-25)). Unsurprisingly, the district court did not rely on Dr. Myerson's impeached trial testimony to support its finding.

Regardless, there is no evidence of any "deviations" by Regis. The term "deviation" carries scientific significance to describe when a synthetic process is altered. Appx1808(295:3-13) (Lepore). For example, Girindus altered its process compared to Brown in six different ways, and each was labeled a "deviation." Appx2248; Appx1808(295:2-299:9) (Lepore discussing Appx3157-3168 (DTX-62)); Appx2033(791:5-23) (Myerson). Unlike Girindus, no document ever identifies any Regis "deviations." Appx1819(337:22-338:19) (Lepore). Even if Regis had made "changes," they would have been "extremely minor things"; otherwise, they would have been identified as "deviations." Appx1819(338:1-3, 14-19); Appx1874(364:3-365:13).

Exelixis also argues that even if Regis followed Brown, Regis's "three samples would be insufficient to prove inherency." Br. 59-60. But this Court's case law does not require additional samples. All that is required is "the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020). Exelixis did not dispute that experimental data showed that the Regis batches were all essentially free of the 1-1 impurity. Appx49.

And unrebutted expert testimony showed that was the natural result of Brown. *Infra* 34-35; Appx1874(366:14-18) (Lepore). In failing to find inherency, the district court clearly erred.

B. The district court clearly and legally erred in requiring MSN to show that the 1-1 impurity does not form through degradation.

Exelixis' argument that "the 1-1 impurity could and did form via degradation" (Br. 55-56) does not support the district court's judgment. Claim 3 of the '349 patent does not exclude the 1-1 impurity *entirely* or prohibit *any* degradation. Rather, the "*essentially* free" limitation undisputedly *allows* up to 200 ppm of the 1-1 impurity, without any restriction on the "route by which the 1-1 impurity form[s] in the API." Br. 61. Yet the district court demanded more than the claim requires by holding it was MSN's "burden [] to show that the Brown process *does not form* the 1-1 impurity through degradation." Appx51. This was legal error"—requiring a "standard of proof[] which is too exacting." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005).

This Court has repeatedly cautioned against "introduc[ing] a limitation … beyond what is expressly recited by the claims." *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1254 (Fed. Cir. 2014) (reversing

and holding asserted claims anticipated). Exelixis argues that MSN "failed to show that the impurity would *not* form[] by degradation," which is "evidence alone [that] sufficiently supports the district court's finding" of nonobviousness. Br. 5, 61. But whether Brown results in *no* impurity formation by degradation—an unclaimed feature—is "irrelevant to the analysis." *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 843 F.3d 1315, 1337-38 (Fed. Cir. 2016) (reversing and holding that a distinction over the prior art was "irrelevant to the analysis" because "[n]othing in the claims requires [that distinction]."). "All that matters" is that Brown naturally results in cabozantinib essentially free of the 1-1 impurity. *Id.*

The distinction Exelixis draws to *SmithKline* is illusory. Br. 64. Exelixis attempts to sidestep the district court's improper application of a "standard of proof [that] was 'too exacting'" by arguing that "it would have been sufficient for the defendant to show that [the claimed product] was 'the natural result flowing from the operation as taught in the prior art.'" Br. 64 (citing *SmithKline*, 403 F.3d 1331). But that distinction supports MSN's position. MSN did not have "to show that the Brown process does not form the 1-1 impurity through degradation." Appx51. MSN

merely needed to show that Brown "naturally results in the production" of API essentially free of the 1-1 impurity. *SmithKline*, 403 F.3d at 1344. As explained, MSN did so. Opening Br. 61-65.

Requiring MSN "to show that the Brown process *does not form* the 1-1 impurity through degradation" (Appx51) also contradicts the specification. The '349 patent teaches that the "[1-1] is a byproduct that *may form* during the synthesis of [cabozantinib]." Appx86(22:8-27). "[T]he disclosure" of the '349 patent merely describes a process for "[m]inimizing the concentration of [] byproducts such as the [1-1]," not preventing formation of the 1-1 altogether, as the district court required. *Id*. Not even Exelixis claims to have invented a process that eliminates degradation, merely touting that its "B-2 Process [described in the '349 patent] successfully *reduced* formation of the 1-1 impurity." Br. 12-13.

C. Exelixis' evidence regarding the "A-2" process, which includes the Girindus batch that deviated from Brown, do not support the judgment.

Contrary to Exelixis' argument, MSN is not asking this Court to "assume" anything about the Regis or Girindus batches. Br. 63 (emphasis omitted). Rather, MSN is relying on the testing and testimonial evidence presented at trial showing that Regis followed the Brown process,

whereas Girindus did not. It was "undisputed" that the three Regis "batches all … met the 'essentially free' limitation." Appx49. Conversely, the single Girindus batch did not. Appx49 n.13. Nor has MSN asked this Court to "assume that the 1-1 impurity necessarily did not form … above 200 ppm." Br. 63 (emphasis omitted). Again, the testing evidence showed that when Regis prepared API pursuant to the Brown process, it obtained material essentially free of the 1-1 impurity. Appx49.

Exelixis relies on misdirection—conflating the "A-2," "Regis" and "Girindus" processes—to distort the factual record over what occurred during the Brown process. Br. 55-56, 63. Exelixis lists four bullet points of supposed "evidence that the 1-1 impurity formed … as a degradant during the Brown process." Br. 55-56 (citing Appx1925, Appx10845, Appx1933, Appx1956). These citations do not address the Regis/Brown process alone, however, but instead generically reference the "A-2 Process," which lumps the Regis and Girindus batches together. Appx3219 (both manufacturers use process "A-2").

Regis followed the Brown process (*supra*, § II.A), so those batches "that were produced … using the [prior art] method" are relevant to the inherency inquiry. *3form, Inc. v. Lumicor, Inc.*, 678 F. App'x 1002, 1009-

10 (Fed. Cir. 2017). Girindus, on the other hand, deviated six times from Brown. Appx2248; Appx1808(295:2-299:9) (Lepore discussing Appx3157-3168 (DTX-62)); Appx2033(791:5-23) (Myerson). Because Girindus did not use the method disclosed in [the prior art]," Exelixis' evidence from the A-2 Process (which includes the Girindus data) can be disregarded since it is not probative of what would inevitably occur if Brown were followed. *3form*, 678 F. App'x at 1010 n.3.

Exelixis again relies on evidence regarding the "A-2 Process," arguing that the district court "credited Dr. Myerson's testimony that [the degradation] problem persisted during the A-2 Process." Br. 61 (citing Appx1956(693:3-13, 694:5-12). But this testimony fails to support the judgment for two reasons. First, because it generally relates to the A-2 Process, it again includes the Girindus batch, which did not follow Brown. Appx3219. Second, Exelixis ignores Dr. Myerson's ultimate conclusion that any 1-1 impurity remaining at the end of the Brown process would be expected to be "at most, de minimis." Appx46 (citing Appx2013(709:5-19) (Myerson)). This opinion was reinforced by Exelixis' Nobel prize winning chemist, Dr. MacMillan, who testified that there would be "no

impurity" expected "at the end" of the Brown process. Appx52 (citing (668:16-669:14) (MacMillan)).

In short, Exelixis argued that a POSA "would not think any 1-1 impurity [by degradation or any other route] would be left at the end of the Brown process." Appx53. The district court agreed and found that the scientific evidence at trial showed that "there is, at most, a de minimis amount of the impurity left after the Brown process." Appx53; *see also* Appx46 (¶¶ 10, 12).

The district court further found that a POSA would not have been motivated to minimize the 1-1 impurity because the POSA would have "already controlled the impurity" by "following the Brown process." Appx53. The district court credited this evidence and Exelixis' arguments to reject MSN's alternative obviousness argument. Appx52-53. But those very same findings, if credited, undermine the district court's inherency finding. The district court's contradictory finding for purposes of inherency that "the 1-1 impurity can form as a degradation product during the Brown process" is clearly erroneous. Appx46(¶ 8). Even if some 1-1 could form through degradation, there was no evidence below that following the Brown process resulted in 1-1 levels above 200 ppm. The evidence

was entirely to the contrary. As explained, based on the underlying science, a POSA would not have expected 1-1 to exist at anything other than de minimis levels, and the Regis testing proved that the Brown process resulted in cabozantinib that was essentially free of the 1-1 impurity.

For all these reasons, the district court committed both legal and clear error.

CONCLUSION AND RELIEF SOUGHT

The Court should reverse the district court's judgment that the asserted claims are not invalid. The Court should hold that the malate salt patents' asserted claims are invalid for lacking written description, and the '349 patent's asserted claim is invalid for obviousness. Alternatively, the Court should at least vacate the judgment against MSN's invalidity defenses and remand for the district court to consider those defenses under the correct legal standards.

Respectfully submitted,

/s/ Bryce A. Cooper

EIMERIC REIG-PLESSIS
Winston & Strawn LLP
101 California Street
San Francisco, CA 94111
(415) 591-6800
ereigplessis@winston.com

KURT A. MATHAS
BRYCE A. COOPER
KEVIN J. BOYLE
Winston & Strawn LLP
35 W. Wacker Drive
Chicago, IL 60601
(312) 558-5600
kmathas@winston.com
bcooper@winston.com
kjboyle@winston.com

Counsel for Defendants-Appellants MSN Laboratories Private Ltd. and MSN Pharmaceuticals, Inc.

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/s/ Bryce A. Cooper
BRYCE A. COOPER
Counsel for Defendants-Appellants

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